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EXAMINER	
SALMON, KATHERINE D	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/686,619	O'TOOLE ET AL.	
	Examiner	Art Unit	
	KATHERINE SALMON	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,8,22 and 23* is/are pending in the application.

4a) Of the above claim(s) *4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 5, 8, 22-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/18/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Its DETAILED ACTION

1. This action is in response to papers filed 3/18/2009.

2. Currently Claims 1-2, 4-5, 8, 22-23 are pending. Claims 3, 6-7, 9-21 have been cancelled. Claim 4 has been withdrawn as being drawn to a nonelected invention.

3. The following rejections to Claims 1-2, 5, 8, 22-23 are necessitated by amendment. Specifically the 35 USC 112/Scope of enablement has been amended to address the newly presented claim 23. Response to arguments follows.

4. This action is FINAL.

Reiterated Rejections

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-2, 5, 8, and 22-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method of identifying an increased likelihood of lupus nephritis in a mouse, the method comprising the steps of:

a) Obtaining a kidney sample from a control mouse and a mouse of interest

b) Detecting an expression level of the midkine mRNA transcript in the kidney sample of the control mouse and the mouse of interest

c) Comparing the midkine mRNA transcript level of the control mouse and the mouse of interest, wherein an increased expression level of the midkine mRNA transcript level of the mouse of interest relative to the expression level of the midkine mRNA transcript level indicates that the mouse of interest has an increased likelihood of lupus nephritis,.

does not reasonably provide enablement for methods to diagnose lupus nephritis (LN) in human by detecting an elevated expression level of midkine gene. Further the instant specification does not reasonably provide enablement for a method of preventing lupus nephritis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims

The claims are broadly drawn to diagnosing lupus nephritis in a human or a mouse comprising detecting the expression level of midkine gene in a kidney sample wherein an elevated expression level indicates an increased likelihood of lupus

nephritis. The claims are broadly drawn to include methods where both human and mouse are subjects.

The claims are broadly drawn to administering an agent to treat or prevent lupus nephritis.

The invention is in a class of inventions that the CAFC has characterized as "the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification

The specification teaches systematic lupus erythematosus (SLE) is an autoimmune disease that has diverse and variable clinical manifestations that range from skin rash and joint pain that can show spontaneous remissions to severe kidney disease that may result in renal failure, otherwise known as lupus nephritis (LN). Midkine (MDK) has several functions including neural-glial interactions in brain development, inflammation, tumor and angiogenesis, and anti-apoptotic activities (specification, pages 14-19). The specification asserts that midkine is a marker for SLE or LN, and its expression can be utilized as a diagnostic for said diseases (page 4). The specification concludes "MDK has not previously been associated with SLE and LN…..While mouse models were used for the initial differentiation expression analysis; it is well-appreciated that animal models can be interpreted to reflect expression levels from human subjects as well. The present invention…encompasses human MDK" (page 22). The specification further asserts "without limitation as to mechanism, the present invention is based in

part on the principle that modulation of the expression of the MDK gene expression may ameliorate SLE/LN, when they are expressed at levels similar or substantially similar to normal non-diseased tissues" (page 23).

The specification discloses working examples of the isolation of RNA from kidney samples of several different mouse models of lupus that ranged in age of five months to 8, 16, 20 weeks of age, thus representing early, intermediate, and late stages of lupus, and control mice of the same age range. The working examples disclose that after the isolation of kidney tissues from said mice, RNA was isolated and cDNA was synthesized, and then the samples were analyzed with Affymetrix Mu11KsubA and Mu11KsubB microarrays. Statistical analysis was subsequently performed, and TaqMan assays were performed on genes of interest (pages 13-14 and 78-82).

With regard to Claim 23, while the instant specification teaches several known treatments for lupus (paragraph 12 p. 3) the art is silent with regard to a agent which prevents lupus nephritis. Further the specification provides no guidance or working examples of any agent for preventing lupus nephritis.

State of the Prior Art

Kotzin et al. teaches (Cell, 1996, Vol. 85, pages 303-306) the underlying cause of lupus has yet to be determined as environmental factors such as sun exposure, viral or bacterial infections, hormonal and drug treatments, and genetic contributions play a role in the manifestation of the disease (Kotzin, page 305). Kotzin teaches several animal models have been used to study lupus, however, due to the complex nature of the disease, "even when one animal model and one phenotype is considered, the genetic

basis of lupus-like disease is remarkably complex, involving contributions from multiple genes in addition to class II MHC….Furthermore, it seems likely that different genetic contributions are operative in different animal models (and therefore in different patients), even when the same phenotype is being followed" (page 305). Kotzin further teaches mouse models are used to study the genetic causes of lupus, and to predict human genes that are associated with said disease since mouse and human genes are homologous (Journal of Clinical Investigation, 1997, Vol.99, No. 4, pages 557-558). However, as stated above, environmental factors and phenotypic expression of lupus have considerable variation, and since the environment conditions are controlled for animal studies and the animal models are bred to have uniform lupus symptoms, it is unclear if results from animal studies can be applicable to humans. Kotzin teaches, "disease phenotype among mice in each cross is much more uniform compared to the relatively heterogeneous disease expression in patients. Especially in SLE, clinical manifestations and autoantibody production can be extremely diverse and variable, which is in part genetically based, and this variability can confound genetic studies" (Journal of Clinical Investigation, page 557). To ensure accurate predictions of the results of mouse lupus models to humans "there should also be concern that an initial mapping in a complex trait reflects false positive readings….If true, this human locus…may not be in a region synthenic to the murine susceptibility locus, and linkage in the current human study would therefore represent quite a fortuitous finding," and in order to ensure accurate results, large studies of human patients will need to be performed (Kotzin, Journal of Clinical Investigation, page 558).

The Relative Skill of Those in the Art

The level of skill in the art is deemed to be high.

The Predictability or Unpredictability of the Art and Degree of Experimentation

Moreover, as indicated by Kotzin et al., an animal model may not be an accurate representation of another animal's response to lupus. Genetic homology does not necessarily correlate to phenotypic expression. As mentioned previously, environmental factors play a role in the development of lupus, and it is unpredictable if a mouse, particularly in a controlled environment, will react in the same manner to environmental factors as humans.

Liu et al. (Clinical Immunology 2004 Vol. 112 p. 225) teaches that that correlation of genes to disease traits in mouse models is not indicative of correlation in humans. Liu et al. teaches that the gene expression profile of humans with autoimmune disease is not the same as the gene expression in a mouse model and in fact there is very little overlap in the gene expression profile of the two (Abstract). Liu et al. found that there was no overlap between the differentially expressed genes between human and mouse data sets with regard to systemic lupus (p. 228 1st column 1st paragraph). Liu et al. teaches that their results show that murine models do not perfectly model corresponding human autoimmune diseases when gene expression profiles are considered (p. 229 2nd column last paragraph).

Morel et al. (PLOS Biology August 2004 Vol. 2 p. 1061) teaches that one cannot directly apply data obtained from animal models to human diseases (p. 1062 1st column last paragraph). Morel et al. teaches that human autoimmune diseases (which includes lupus) show extremely heterogeneous clinical presentation and that animal models only present a simplified version (p. 1062 1st column last paragraph). Morel et al. teaches the mouse model only provides a partial representation of the real biological complexity underlying the human disease (p. 1062 1st column last paragraph). Morel et al. teaches that extrapolation from animal models to autoimmune patients are limited by the differences between the two immune systems (p. 1062 2nd column 1st paragraph).

Consequently, it is unpredictable if a mouse phenotypic expression of lupus will be similar to humans. Consequently, the skilled artisan would have to examine midkine's expression in As a result, the specification does not teach the person skilled in the art how to reasonably predict, without undue burden, SLE or LN by midkine expression levels in a biological sample of human.

Enard et al. (Science 2002 Vol 296 p. 340) teaches that even between closely related species gene expression patterns differ (abstract). Enard et al. teaches that mRNA expression levels are different between humans, chimpanzees, orangutans and rhesus marcques (p. 340 1st column last sentence-2nd column 1st paragraph). Enard et al. teaches that there are a large number of quantitative differences in gene expression in closely related mammals (p. 342 2nd column last paragraph). Therefore the art teaches that even between very closely related mammals there is a divergence of gene expression.

Amount of Direction or Guidance Provided by the Specification

Though the specification provides working examples of mouse models with regard to the detection and correlation of elevated expression levels of midkine gene, the specification has not provided sufficient guidance to extrapolate these results to human. Further the art teaches that correlations in mouse models are not sufficient to correlate expression in humans. The art also teaches that expression profiles of genes differ in humans afflicted with autoimmune disease and mouse models with autoimmune disease. Therefore the specification has not provides sufficient guidance to one skilled in the art to correlate elevated midkine levels to lupus in humans. Further the skilled artisan would have to perform undue experimentation to correlate midkine levels with lupus in humans because the art teaches that correlations in mouse models cannot be extrapolated to humans without intervening experimental steps, which have no guarantee of success.

Working Example

The specification does not provide working examples of methods to diagnose lupus with midkine expression levels in human. The methods do not demonstrate the methodology can be used to predictably diagnose lupus with midkine mRNA in humans.

Conclusions

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright 990 F.2d 1557, 1561. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in Genentech Inc. v Novo Nordisk 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In view of the high level of unpredictability in the art and lack of guidance provided by the specification and prior art, undue experimentation would be required to practice the claimed invention.

Response to Arguments

The reply traverses the rejection. A summary of the arguments presented in the reply is presented below with response to arguments following.

(A) The reply asserts that Kotzin 1 and Kotzin 2 as cited by the office action teaches that NZB X NZW mice are one of the best studied models of lupus nephritis (p. 3 4th paragraph). The reply asserts that this is the specific mouse model utilized in the present application and Kotzin 1 and Kotzin 2 do not suggest that there is no correlation between midkine gene expression in mice and in humans.

These arguments have been fully reviewed but have not been found persuasive.

Although, Kotzin 1 and Kotzin 2 do not teach midkine expression, these references teach that because lupus is such a complex diseases that the direct extrapolation of expression in a mouse model to a human is unpredictable. Therefore, the art teaches that direct extrapolation, in general, is unpredictable, whereas the instant specification has not provided any evidence that the human expression level in the midkine gene is similar to the mouse. Further although the mouse model used in the instant specification might be the "best" model, art at the time of filing teaches that even with the best model expression level cannot be directly extrapolated.

(B) The reply asserts that Liu et al. does not contemplate the specific mouse model utilized in the present application and as such is not applicable to assert unpredictably (p. 3 last paragraph). Further the reply asserts the declaration submitted by Dr. O'Toole distinguished the present results as involving a particular mouse model that is in fact a good model for lupus (p. 3 last paragraph and p. 4 1st paragraph). It is noted that the declaration the reply is referring to was submitted on 10/23/2007.

These arguments have been fully reviewed but have not been found persuasive.

Again, although the used model might be a good model for lupus, the art as presented above teaches that expression of genes in mouse models are not directly correlative to humans. Further Liu et al teaches that in mouse models there is very little overlap between differentially expressed genes. Although the mouse models might be different between Liu et al. and the instant specification, the art teaches that in general

mouse models expression data must be evaluated in a human subject to make direct correlations between a disease and human.

(C) The reply asserts that Morel et al. is irrelevant because Morel et al. does not discuss midkine gene expression, but rather that human autoimmune disease are extremely heterogeneous clinical presentation and that animal models only present a simplified version (p. 4 1st full paragraph).

These arguments have been fully reviewed but have not been found persuasive.

Although it is acknowledged that Morel et al. does not discuss midkine gene expression, Morel et al. teaches that human autoimmune disease are extremely heterogeneous clinical presentation and that animal models only present a simplified version. Herein in the instant application, the applicants have not bought in any data, or any data present in the instant specification or data in the art at the time of filing, that midkine expression in a mouse model is similar to expression in a human with lupus.

(D) The reply asserts that Enard et al. only compares gene expression patterns between different species, but does not show that the genes were differentially expressed between healthy and lupus disease individuals of the same or of different species (p. 4 2nd full paragraph).

These arguments have been fully reviewed but have not been found persuasive.

However, Enard et al. was placed on record to disclose that expression patterns between closely related animals can differ. Herein in the instant case, the application is

trying to correlate one expression pattern in one animal (mouse model) to another animal (e.g. a human). However, neither the specification or the art at the time of filing shows that these two expressions are the same.

(E) The reply asserts that in addition to the declaration of Dr. O-Toole, applicants provide Kosugi et al. which the reply asserts teaches that the midkine gene expression in mice correlates with autoimmune disease in humans (p. 4 3rd full paragraph). The reply asserts that the teachings of Kosugi et al. teaches that the midkine gene expression in mice correlates with autoimmune disease in humans and therefore the expression patterns in a mouse model can be extrapolated to humans (p. 4 5th full paragraph).

These arguments have been fully reviewed but have not been found persuasive.

It is noted that Kosugi et al. is postfiling art which shows MK expression was detected in diabetic nephropathy human samples (p. 906 1dt column 2nd paragraph). However, the art makes no comment about the association of expression levels in lupus patients and correlations to the midkine expression. As discussed in previous office actions, autoimmune diseases are a vast array of diseases wherein each disease has a different set of genes expressed. Herein in the instant case, although in postfiling work expression of the midkine gene was similar in the mouse model for diabetic nephropathy and humans, this work does not provide evidence that lupus associations would be similar.

(F) The reply asserts that in response to the argument that there is no support that the mTOR pathway correlates with lupus, Applicants have included Reddy et al. (p. 4 4th full paragraph). The reply asserts that Reddy et al. teachings that their findings implicate the mTOR pathway is a critical contributor to human lupus (p. 4 4th full paragraph).

These arguments have been fully reviewed but have not been found persuasive.

Though this postfiling art shows that mTOR pathway is a contributor to human lupus, this art does not provide evidence that expression patterns of the midkine gene in a mouse model is correlative to a human expression patterns. Although both the mouse and the human might have the same genes in the functional pathway, the mouse model is a simplified version of the human system. As such correlations in expression in a mouse model is not directly extrapolated to a human, without evidence that such expression level is similar between the two. Because the mouse model is only a simplified version of the human system, all the potential gene interactions are not observed in the mouse model. As such, expression levels which appear high in a mouse model are not directly correlative to high expression in a human.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHERINE SALMON whose telephone number is (571)272-3316. The examiner can normally be reached on Monday-Friday 8AM-530PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Katherine Salmon/
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